Journal of Advances in Medicine and Medical Research

Volume 36, Issue 2, Page 97-112, 2024; Article no.JAMMR.112979
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Coronavirus in Pregnancy: The Role of Melatonin

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Authors' contributions

This work was carried out in collaboration between both authors. Authors GL designed the study and wrote the manuscript. Author JdeOM managed the literature searches and wrote the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2024/v36i25371

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/112979

Review Article

Received: 05/12/2023
Accepted: 10/02/2024
Published: 16/02/2024

ABSTRACT

The effects of COVID-19 on pregnant individuals are unclear due to a series of physiological changes and immune system adaptations that may affect the development of the fetus. There is evidence supporting the role of melatonin in human pregnancy, and it appears that melatonin is essential for a successful pregnancy. However, in pathological conditions, such as during SARS-CoV-2 infection, melatonin levels can be significantly inhibited. In addition, melatonin, a powerful endogen antioxidant, free radical scavenger, and anti-inflammatory molecule, has been reported to exert beneficial effects on viral diseases such as COVID-19. This review focuses on the current evidence regarding the physiopathology of COVID-19 in pregnancy conditions, the role of melatonin during pregnancy, and the use of melatonin as a promising treatment. Addressing these points should help us understand the knowledge currently available about COVID-19 during pregnancy and explore the possible beneficial effects of melatonin. Physiological and immunological adaptations during pregnancy may result in systemic effects that greatly contribute

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to the development of acute viral infectious diseases such as COVID-19. Melatonin as an adjuvant in COVID-19 treatment has anti-inflammatory, anti-oxidative, and immune response regulatory functions. The strategy that melatonin offers is to slow the cytokine storm observed and reduce oxidative damage to enhance the resistance of individuals and provide additional survival time. Although the direct evidence of melatonin application in COVID-19 is unclear, both its use in experimental animal models and studies on humans has consistently documented its efficacy and safety, and its use by COVID-19 patients would be highly beneficial.

Keywords: COVID-19; melatonin; pregnancy.

ABBREVIATIONS

COVID-19 : Coronavirus Disease-2019
SARS-CoV-2 : Severe Acute Respiratory Syndrome Coronavirus 2
Ang II : Angiotensin
ACE-2 :Angiotensin-Converting Enzyme 2
IL-18 : Interleukin-18
IL-6 : Interleukin-6
IL-8 : Interleukin-8
IL-20 : Interleukin-20
IL-12 : Interleukin-12
IL-1β : Interleukin -1β
CXCL : Motif Chemokine Ligand
TNF-α : Tumor Necrosis Factor α
Th1 cells : Type 1 T helper
TMPRSS2 : Transmembrane Serine Protease 2
RNA : Ribonucleic Acid
N : Protein Nucleocapsid
M : Protein Membrane
E : Protein Envelope
S : Protein Spike
IFN-β : Interferon beta
IFN-λ : Interferon gama
ARDS : Acute respiratory distress syndrome
AT2R : Ang II receptor 2
ROS : Reactive Oxygen Species
MT1 and MT2 : Metallothionein 1 and 2
SNAT : Serotonin-N-acetyltransferase
HOM : Hydroxyindole-O-Methyltransferase
NF-E2 : Nuclear Factor Erythroid 2
NF-κB : Factor Nuclear Kappa B
IUI : Intrauterine Inflammation
LPS : Lipopolysaccharide

1. INTRODUCTION

"The World Health Organization declared the coronavirus disease-2019 (COVID-19) pandemic on March 11, 2020" [1]. "At that time, the origin of the disease was yet unclear, but it was known that infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exacerbated respiratory inflammation, resulting in pulmonary oxygen exchange deficit and severe pneumonia" [1]. "Alterations in the levels of immune cells, including lymphocytes and thrombocytes, and some C-reactive proteins, lactate dehydrogenase enzymes, and angiotensin (Ang) II are seen in COVID-19 patients" [2].

"The effects of COVID-19 on pregnant individuals are unclear due to a series of physiological changes and immune system adaptations that regulate the development of the fetus" [2]. "During pregnancy, the respiratory, circulatory, endocrine, reproductive, and immune systems are subject to many changes that may affect the

body's responses to viral infections. Such responses may not be observed in non-pregnant individuals" [3]. "The immune response to SARS-CoV-2 infection and the pathophysiology and molecular mechanisms of the disease are yet to be understood" [4].

"Pregnant people represent a high-risk population due to a decrease in the number and activity of lymphocytes during late gestation, which may affect the viral clearance rate and delay the viral infection deterioration" [5]. "It has also been demonstrated that angiotensin-converting enzyme 2 (ACE-2), a SARS-CoV-2 receptor, is highly upregulated during pregnancy, which may contribute to increasing the susceptibility of this population to SARS-CoV-2" [6]. "More importantly, fetuses and newborns are highly susceptible to infections due to their immature innate and adaptive immune systems" [7]. "Dysregulation of factors such as cytokines and the complement cascade caused by infections may have deleterious consequences for brain development and function in fetuses and newborns" [8].

"There is evidence supporting the role of melatonin in human pregnancy; melatonin appears to be essential for successful pregnancy" [9]. "However, in pathological conditions such as during SARS-CoV-2 infection, melatonin levels can be significantly inhibited" [10]. "Moreover, melatonin permits the transmission of maternal photoperiodic information to generate day/night differences in the fetus and circadian organization during development, which is essential for the maturation of the fetal biological clock" [11]. "In addition, melatonin, a powerful endogen antioxidant, free radical scavenger, and anti-inflammatory molecule, has been reported to exert beneficial effects on viral diseases such as COVID-19" [12].

Despite this evidence, there are no studies on the effects of this indoleamine on pregnancy conditions. Therefore, adequate information about the relationship between COVID-19 and pregnancy is required for better management of these patients. Herein, we review the current evidence for the role of melatonin in the treatment of COVID-19 in human pregnancy.

2. PHYSIOLOGICAL CONDITIONS DURING PREGNANCY

The physiologic and immunologic adaptations during pregnancy may result in systemic effects

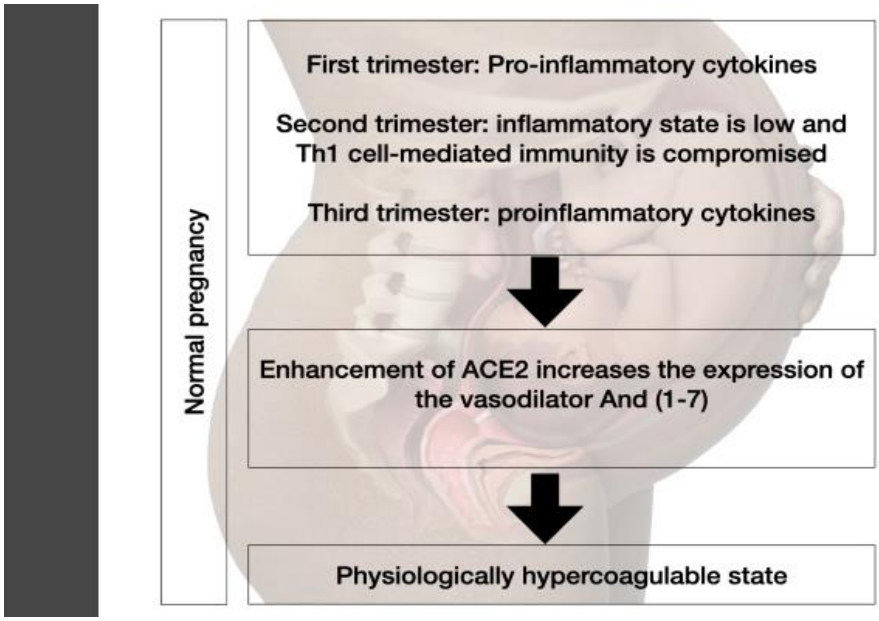

Fig. 1. The physiology of pregnancy

Maternal serum pro-inflammatory and anti-inflammatory cytokine levels are regulated during pregnancy. At the first trimester, embryo implantation and placentation benefit from systemic pro-inflammatory cytokines. In the second trimester, the inflammatory state is low and Th1 cell-mediated immunity is compromised. The inflammatory cytokines are presented in the third trimester

that determine the susceptibility and severity of respiratory infections (Luo, Yin. 2020). “Moreover, rather than immunosuppression, a successful pregnancy requires a robust, dynamic, and responsive immune system” [13].

“During pregnancy the levels of pro-inflammatory and anti-inflammatory cytokine are tightly regulated” [13]. “At first, embryo implantation and placentation benefit from systemic pro-inflammatory cytokines such as C-X-C motif chemokine ligand **(**CXCL), tumor necrosis factor α (TNF-α), Interleukin (IL)-18, IL-6, and CXCL8, after which an anti-inflammatory state leading to angiogenesis and enhancing fetal growth. Then, a subsequent pro-inflammatory state prepares for the initiation of labor in the third trimester” [13,14]. “In addition, during the second trimester, the inflammatory state is low and Th1 cell-mediated immunity is compromised” [13,15], thus “increasing the susceptibility of pregnant women to viral and bacterial infections” [13,15]. “Finally, pregnancy could be considered a physiologically hypercoagulable state with raised coagulation factors, fibrinogen and factor VIII included and decreased fibrinolytic proteins” [16].

3. PHYSIOPATHOLOGY OF COVID-19

SARS-CoV-2 is transmitted via respiratory aerosols [17]. Viral particles are inhaled and bind to nasal mucosa, infecting the epithelial cells [17,18]. In the nasal epithelium, both ciliated and mucus-secreting cells express ACE2 and TMPRSS2 leading to SARS-CoV-2 releasing their RNA inside these cells [19]. It is important to note that the coronavirus is made up of four main structural proteins: the nucleocapsid (N), membrane (M), envelope (E) and spike (S) proteins [20]. The S protein of coronaviruses facilitates viral entry into target cells [21], the S1 subunit attaches onto ACE2 and the S2.

Subunit binds the S protein to the membrane [22]. The S2 subunit also mediates the mechanism to infect new cells [22]. The main mechanism is by TMPRSS2 activation but the cleavage of S2' site can be provided by cathepsins [20]. If there is not enough TMPRSS2 expressed or the virus-ACE2 complex is unable to bind, the virus is internalized iva endocytosis and into the late endolysosome the S2' site is then cleaved by cathepsins [23,24]. The disease progression is related to infected ciliated cells shedding their ciliary axonemes, which disables mucociliary clearance [25,26]. These infections could be asymptomatic or could cause local symptoms [18].

The virus replicates and releases RNA for further infection of neighboring cells, spreading from the nasal passage to the upper respiratory tract [27].

The immune response is intensified due to the release of CXCL10, IFN-β and IFN-λ from the infected cells and leading to symptoms of fever, malaise, and dry cough [28]. A great number of patients do not progress do not progress farther than this stage because the immune system is able to contain the infection [29].

The next stage of the disease occurs after the virus enters the conducting airways, likely by microaspiration of pharyngeal secretions [30]. The virus then invades and enters the lower respiratory tract via the host’s ACE-2 receptor and starts replication to produce more viral nucleocapsids [29]. The infected pneumocytes release IL-1, IL-6, IL-8, IL-120, and IL-12, TNF-α, IFN-λ and IFN-β, CXCL10, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1α [29].

The amount of cytokines released attracts immune cells such as neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells, then becoming concealed in the lung tissue [29]. The constant apoptosis of the infected cells releases new viral particles that infect the adjacent type 2 alveolar epithelial cells [31], leading to persistent tissue injury and alveolar damage, resulting in acute respiratory distress syndrome (ARDS) [32]. In ARDS, pulmonary endothelial cells contribute to the start and broadcast of this condition by changing vessel barrier integrity, supporting a pro-coagulative condition, inducing vascular inflammation, and reconciling inflammatory cell infiltration [17]. It should be noted that the majority of COVID-19 patients who die succumb to ARDS [29].

Many other pathways are also involved in the progression of the cytokine storm in COVID-19 patients, such as dysfunction of the RAS due to the downregulation of the ACE-2 receptor by binding of the S-protein of SAR-CoV-2 with ACE2 [33]. Notably, the RAS plays an important role in severe acute lung injury because ACE-2 plays a role in lung protection [33]. Since ACE-2 catalyzes the degradation of Ang II into Ang, low levels of ACE-2 increase Ang II levels, which in turn causes AT1R stimulation and Ang II receptor 2 (AT2R) inactivation [33]. AT1R is involved in functions including aldosterone, vasopressin, and adrenocorticotropic hormone secretion,

potassium levels, sodium reabsorption, inflammation, cell proliferation, and lung injury, whereas AT2R has a lung-protective function [33]. Due to the imbalance between these two receptor functions, the actions of AT1R dominate and result in lung injury and hypokalemia [33]. Thus, cytokine storm and ACE-2 downregulation lead to pulmonary vascular hyperpermeability and pulmonary edema, inducing ARDS [33]. An increase in vascular permeability due to clot formation occurs, which leads to multiorgan damage and death [33].

4. COVID-19 IN PREGNANCY

SARS-CoV-2 infection in pregnant women can entail several obstetric complications such as thrombosis, poor development of vasculature, premature rupture of the fetal membrane, deposition of fibrin within the fetal vasculature, and vascular malperfusion of the fetus [34]. Notably, obstetric complications in COVID-19 can be induced by both direct viral effects (e.g., via ACE-2 receptors and viral replication) and subsequent hyperinflammatory responses [35].

COVID-19 induces hypercoagulability that results from the concurrent activation of clot and fibrinolytic cascades, causing both thrombus and clotting factor consumption [36]. Thus, the manifestations can be either thrombotic or hemorrhagic [37,38]. Thrombosis has similarly been reported in pregnant women and the general population [39]; however, pregnant women are more likely to suffer from thrombotic-hemorrhagic catastrophic events [40,41].

SARS-CoV-2 can impact the developing fetus as a result of vertical transmission or indirectly by a viral infection of the placenta [42]. Evidence of viral presence in the human placenta has been reported in the syncytiotrophoblast layer of the chorionic villi [43-45]. Previous studies have demonstrated that the virus in inducing immune responses causes fetus rejection and placental compromise, resulting in placental inflammation [46]. Thus, the fetal inflammatory syndrome can occur due to the mother's response to infection, promoting a fetal inflammatory response with high levels of inflammatory cytokines in the placenta [47]. The hyperinflammatory environment has a deleterious effect on fetal neurodevelopment [48] (Fig. 2).

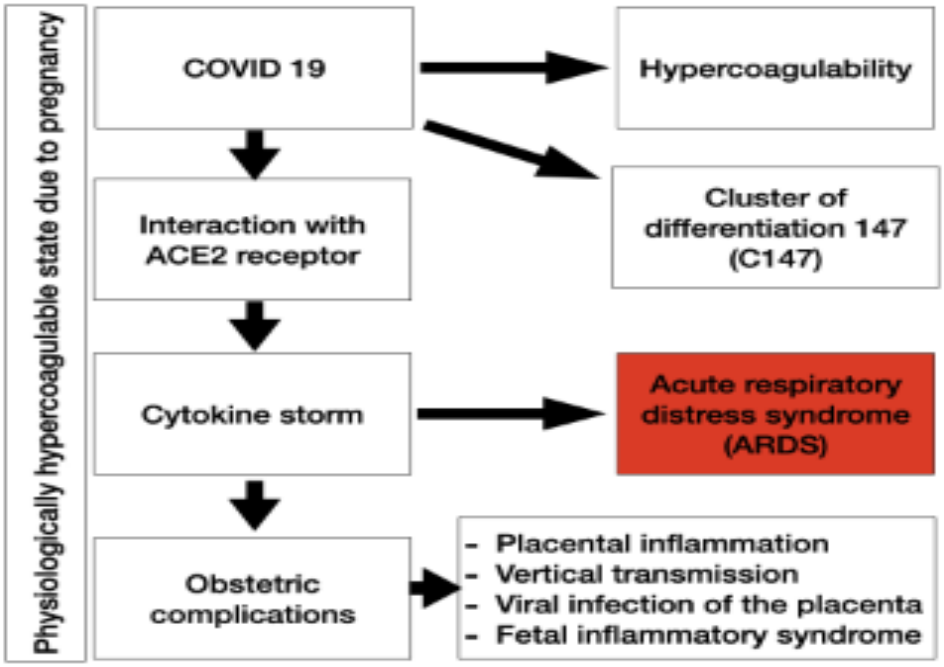

Fig. 2. The SARS-CoV-2 infection in pregnant women

The physiologic and immunologic adaptations during pregnancy may result in systemic effects that determine the susceptibility and severity of respiratory infections. Pregnancy could be considered a physiologically hypercoagulable state with raised coagulation factors. Thus, the SARS-CoV-2 infection in pregnant women can entail several obstetric complications such as placental inflammation, vertical transmission, viral infection of the placenta, fetal inflammatory syndrome. These complications can be induced by both direct viral effects (e.g., via ACE-2 receptors and viral replication) and subsequent hyperinflammatory responses

5. ROLE OF MELATONIN IN PREGNANCY

Melatonin is mainly synthesized and secreted by the pineal gland, but other organs in the reproductive system can also synthesize this hormone [49]. The receptors metallothionein (MT)1 and MT2 were identified in the granulosa luteal cells and the placental villous trophoblasts, and serotonin-N-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HOM) are found in the brain, retinal photoreceptors, immune system, skin cells, and gastrointestinal cells [50]. The main role of melatonin synthesis, through the activation of these receptors in these systems, is to reduce the oxidative damage due to different cell stimuli [51].

Melatonin and cortisol are the main hormones that control the circadian rhythm; however, in pregnant women, estrogen and progesterone levels are also altered in a circadian manner [11]. These two ovarian hormones are secreted during gestation over different temporal patterns. While progesterone levels peak during dark hours, estrogen peaks during the day [52]. Both hormones are produced by the placenta itself, and the uterus also produces estrogen. By producing estrogen, the uterus maintains epithelial proliferation to support implantation and promotes progesterone synthesis by the placenta, which maintains immunosuppressive properties and reduces oxidative damage [53].

The villous trophoblast cells are not only able to produce melatonin but also express MT1 and MT2 receptors, which provide paracrine, autocrine, and intracrine effects in the placenta, thus maintaining a healthy syncytiotrophoblast layer, protecting it from oxidative stress [50]. The placenta also produces the neuropeptide vasoactive intestinal polypeptide [54]. It is known that vasoactive intestinal polypeptide is able to increase SNAT activity and melatonin production and is involved in the control of smooth muscle tissue [54].

This enhanced production increases maternal plasma melatonin, and during the late third semester, the levels of melatonin are at their highest [11]. This may be attributed to the high placental and leukocyte production of reactive oxygen species (ROS). The imbalance between melatonin and ROS levels can lead to pregnancy complications and conditions such as preeclampsia [55].

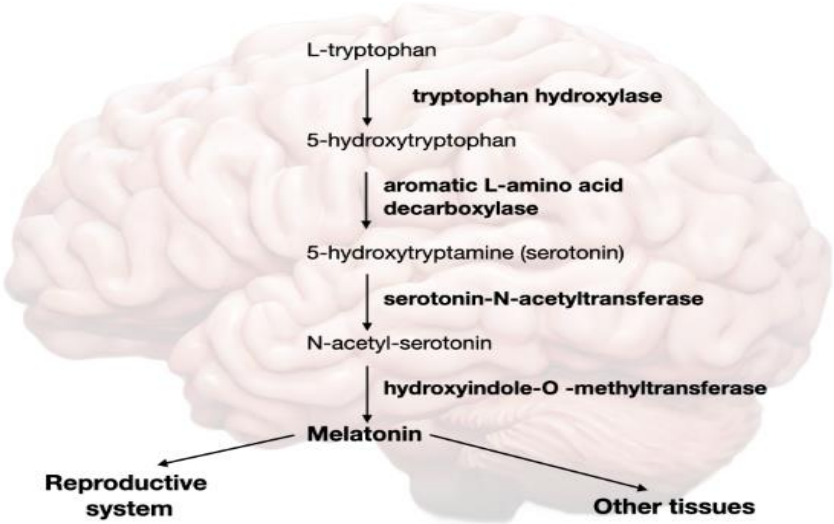

Fig. 3. The melatonin synthesis

Melatonin synthesis depends on dark periods during which the tryptophan hydroxylase enzyme converts L-tryptophan to 5-hydroxytryptophan. Subsequently, 5-hydroxytryptophan is decarboxylated by the aromatic enzyme L-amino acid decarboxylase to form 5-hydroxytryptamine (serotonin). When the light stimulus fades, norepinephrine activates the expression of cAMP, serotonin-N-acetyltransferase (SNAT), and hydroxyindole-O-methyltransferase (HOM). SNAT converts serotonin to N-acetyl-serotonin, and HOM methylates it to melatonin. Melatonin is mainly synthesized and secreted by the pineal gland, but other organs in the reproductive system can also synthesize this hormone

In addition to placental adaptation, melatonin also triggers the fetal system to adjust the circadian rhythm, directly affecting neurodevelopment, and protecting the fetus against ROS [11]. Maternal melatonin oscillations help trigger the fetus' circadian rhythm, and disturbances in this process induce negative consequences in newborn babies [11].

6. MELATONIN AS AN ANTIVIRAL AGENT AGAINST SARS-CoV-2

Melatonin has shown antiviral properties that could help against acute lung injury, thrombosis, sepsis, mortality rate and ARDS induced by bacterial and viral infections [56-58]. Its anti-inflammatory and anti-oxidative properties may be helpful in critically ill patients [12] and may also interact with ACE-2 and B-cell lymphoma 2-like human proteins that are essential for SARS-CoV-2 development [59]. The mechanism of action is illustrated in Fig. 4.

The effects are mediated by melatonin receptors (MTs) that channel the response to hormones throughout the organism [60]. MT1 is distributed in the retina, hypothalamus suprachiasmatic nuclei, pars-tuberalis of the pituitary gland, liver, and skin and is involved in the modulation of brain functions [12,61]. Melatonin can penetrate cells and interact with both the membrane surface and intracellular receptors, resulting in the regulation of pathways responsible for DNA damage responses, tumor metabolism, angiogenesis, and cell signaling [62].

Previous human trials have demonstrated the efficacy of melatonin in the reduction of elevated levels of cytokines in inflammatory pathologies, suggesting that melatonin may be useful in the treatment of COVID-19 [63-67]. A combination of mercaptopurine and melatonin has been suggested to be a potential treatment for COVID-19, acting synergistically to target papain-like protease, ACE-2 and c-Jun signaling, and anti-inflammatory cascades [68]. The possible anti-inflammatory mechanisms of melatonin involve upregulation of sirtuin-1 and suppression of NF-E2-related factor 2, promoting a decrease in the proinflammatory cytokines (TNF, IL-6, IL-10) and an increase in the anti-inflammatory cytokine IL-10 [69]. Previous studies conducted by our group demonstrated the potential melatonin anti inflammatory and analgesic effects in humans and rats [70-76].

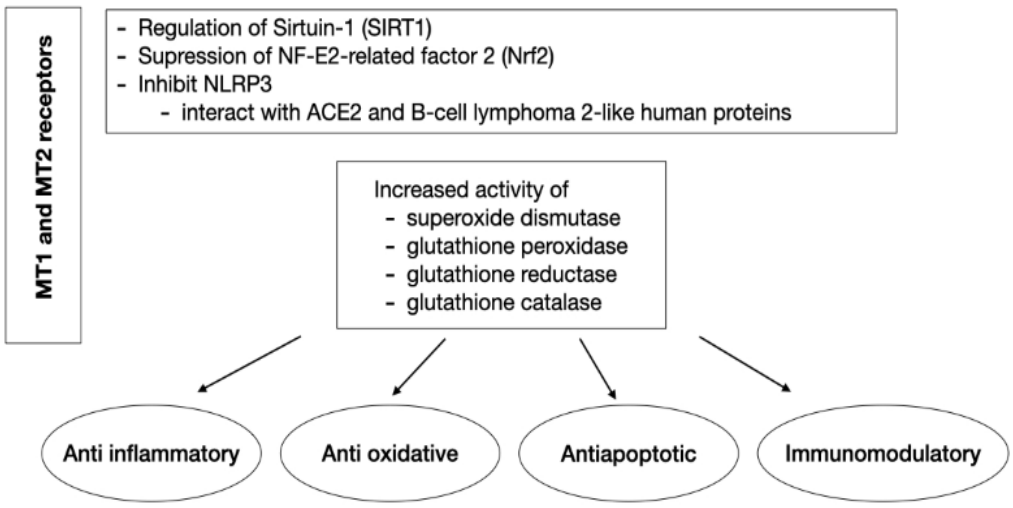

Fig. 4. Effects of melatonin in COVID-19

Melatonin is a promising adjunctive drug for viral infections because of its anti-inflammatory, anti-apoptotic, immunomodulatory, and powerful antioxidant properties. The effects are mediated by melatonin receptors (MTs) that channel the response to hormones throughout the organism. The possible anti-inflammatory mechanisms of melatonin involve upregulation of sirtuin-1 and suppression of NF-E2-related factor 2, promoting a decrease in the proinflammatory cytokines (TNF, IL-6, IL-10) and an increase in the anti-inflammatory cytokine IL-10. Also, it could affect the anti-inflammatory cascades and ACE-2 and c-Jung signaling. Melatonin could inhibit NLRP3 inflammasome protecting macrophages from pyroptosis presented in lung pathology caused in SARS-CoV-2 infection. The antioxidant properties of this indolamine are linked to increased activity of superoxide dismutase, glutathione peroxidase, reductase, and catalase

The antioxidant properties of melatonin may be beneficial in relieving the clinical symptoms of COVID-19 [77]. Melatonin may prolong the survival of infected patients, indicating that the immune system of these patients recovers due to virus elimination [12,78].

In a mouse model of bacterial pneumonia, melatonin was shown to inhibit pneumonia by interfering with the NLRP3 inflammasome, protecting macrophages from pyroptosis [79]. Other studies have indicated that melatonin may be a promising inhibitor of pyroptosis and associated pathologies [79-84].

Other possible indirect effects of melatonin in COVID-19 patients include restoring normal sleep habits and reducing anxiety [85]. Long-term sleep deprivation and/or chronic stress leads to the deterioration of immune functions through the disturbance of barrier mechanisms by suppressing phagocytosis, reducing the proliferation and activity of some leukocytes, in particular CD4þ T cells, while increasing T-suppressors, elevating oxidative stress, and inducing a pro-inflammatory background [86].

7. MELATONIN SUPPLEMENTATION IN PREGNANCY

Melatonin has high biological safety, and exogenous melatonin can be used in a variety of doses, including extreme doses [87]. Despite the lack of long-term studies exploring the clinical safety of exogenous melatonin, some clinical trials show that even at doses higher than physiological concentrations, exogenous melatonin use is safe [87]. Besides, there is evidence that large doses of melatonin do not cause irreversible damage or intolerable side effects, setting the safe margin to 3750 mg/day for a 75kg individual [88].

Melatonin is available in different administration forms and it is not known which routes are ideal for pregnant women [89] in order to consider it a potential interventional and prevention of pregnancy complications due to SARS COV-2 infection [90]. It is essential to research more about pharmacokinetic and pharmacodynamics profile of exogenous melatonin in order to guarantee its safe administration and follow up of babies exposed *in utero* [90].

Maternally administered exogenous melatonin crosses the placenta at or near term, similar to a freely diffusible marker and without significant metabolism [91]. This well described crossing placental barrier, and its binding to MT1 and MT2 placental receptors, reinforces its effects upon fetal development; the role of the mother's own circadian rhythm as the first zeitgeber the fetus is exposed to, which in turn modulates fetal neuroendocrine and immune development, and confers antioxidant protection [92-94]. In addition, Miller et al. found reduced levels of malondialdehyde, which is a placental oxidative biomarker in melatonin supplementation in pregnancy [95].

After the administration, serum melatonin levels peak 2 hours [96] and maternal and fetal concentrations reach equilibrium within 150 minutes [97]. We found no clinical trials whose primary outcomes were the safety and efficacy of melatonin during pregnancy. Three clinical trials used melatonin for conditions during pregnancy such as hyperglycemia [98], preeclampsia [99] and IUGR [96] reported some efficacy for each condition, although sample sizes were small. It is important to note that none of the three trials reported safety concerns or adverse maternal or fetal events related to melatonin administration during pregnancy. The dose used in these studies ranged from 8 to 30 mg daily. The trial with the highest daily dose (30 mg) reported no increased daytime drowsiness, which is an important safety finding [99]. The safety concerns about melatonin use in pregnancy originated from animal studies and include decreased birth weight [100] altered circadian rhythm development [101], and mortality [102].

8. THE ROLE OF MELATONIN IN CORONAVIRUS DURING PREGNANCY

The coronavirus infection in pregnancy induces the production of proinflammatory, antiinflammatory cytokines and oxidized products that activate the maternal immune system and can cross the placental barrier [103-105]. The developing fetus can be impacted directly by viral infection as a result of vertical transmission (i.e. transmission from mother to fetus) or indirectly by viral infection of the placenta [106].

Inhibition of melatonin by most viruses suggests that this indoleamine can be useful in the management of viral infections, such as COVID-19 [107]. Furthermore, melatonin has protective effects against cellular insults that occur perinatally, leading to neuroprotective properties because of the reduction of proinflammatory response caused by the oxidative stress and

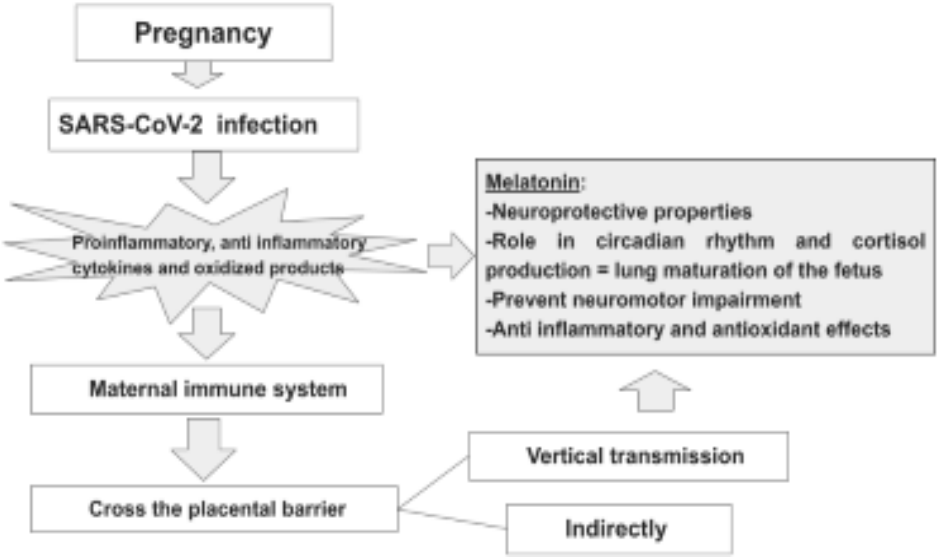

Fig. 5. The role of melatonin in pregnant women with coronavirus

Host response to coronavirus infection in pregnancy induces the production of proinflammatory, antiinflammatory cytokines and oxidized products that activate the maternal immune system and can cross the placental barrier. The developing fetus can be impacted directly by viral infection as a result of vertical transmission or indirectly by viral infection of the placenta. Melatonin has several neuroprotective properties through the reduction of oxidative stress, proinflammatory response and apoptotic cell death. This indoleamine could decrease neuroinflammation and perinatal brain injury, thus preventing neuromotor impairment. Circadian rhythm and melatonin are essential in controlling the endocrine system and metabolism; these systems are involved in the production of cortisol, which plays a key role in lung maturation of the fetus

avoiding apoptotic cell death [108-112]. The melatonin pretreated group showed decreased neuroinflammation and perinatal brain injury with normal neuronal differentiation of neuroblasts in the cortical plate compared to those not pretreated with melatonin [113].

In addition, melatonin prevented the increased apoptotic activity of fetal neurons under hypoxia, possibly induced by a hypercoagulable state as a result of intrauterine inflammation [114]. Melatonin can improve hemodynamics at the maternal-placental interface, which is essential for fetal growth under intrauterine inflammation conditions because of the increased risk of hypoxic-induced brain ischemia from a hypercoagulable state in the placenta [115].

Fetal mice that grew under LPS-induced intrauterine inflammation, when pretreated with melatonin, had lower levels of inflammation (NF-κB, IL-1β) in the placenta and increased expression of silent information regulator 2 homolog 1/nuclear factor erythroid 2-related factor 2 in uterine strips than those not pretreated with melatonin [113]. In another study, pregnant mice pretreated with melatonin before LPS-induced IUI showed significantly reduced inflammatory mediators, and it prevented an increase of the oxidative stress marker (4-hydroxy-2-nonenal) in the placenta [116].

Finally, circadian rhythm and melatonin are essential in controlling the endocrine system and metabolism; these systems are involved in the production of cortisol, which plays a key role in lung maturation of the fetus, and aids the mobilization of glucose and fatty acids from the liver to meet the high metabolic demands of the fetus [11,117] (Fig. 5).

9. CONCLUSION

We have provided an overview of the knowledge currently available about COVID-19 during pregnancy and explored the possible beneficial effects of melatonin.

Physiological and immunological adaptations during pregnancy may result in systemic effects that greatly contribute to the development of acute viral infectious diseases such as COVID-19. It is important to note that obstetric complications in COVID-19 could be induced by both direct viral effects (e.g., through ACE-2

receptors or viral replication) and subsequent hyperinflammatory responses.

Melatonin as an adjuvant in COVID-19 treatment has anti-inflammatory, anti-oxidative, and immune response regulatory functions. The strategy that melatonin offers is to slow the cytokine storm observed and reduce oxidative damage to enhance the resistance of individuals and provide additional survival time. Although the direct evidence of melatonin application in COVID-19 is unclear, both its use in experimental animal models and studies on humans has consistently documented its efficacy and safety, and its use by COVID-19 patients would be highly beneficial.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

Author would like to acknowledge Universidade do Vale do Taquari – Univates.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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